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CEREBRAL CHANGES RELATED TO ANOXIA, WITH REPORT OF A CASE*

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THE cells of the body are said to be suffering from the anoxic state when they cannot obtain, or are unable to utilize, sufficient oxygen to enable them to carry on their normal functions. When subjected to such a state, they will not only temporarily cease to function, but if the oxygen lack is prolonged they will die. Barcroft[1] originally described three types of anoxia:

1. The *stagnant* type, characterized by a reduction of the blood flow through a tissue, although the arterial blood contains sufficient oxygen at proper saturation. It is illustrated by the state of shock due to vasomotor collapse. The same type may occur locally as a result of vascular spasm accompanying, for example, the lodgement of a peripheral embolus.

2. The *anoxic* type, due to an interference with the passage of oxygen from the pulmonary alveolar spaces into the capillaries of the alveolar walls. The hæmoglobin does not acquire its normal saturation. Pneumonia, drowning and inhalation of gases deficient in oxygen are examples of this type.

3. The *anæmic* type, that variety in which the oxygen-carrying capacity of the blood is reduced as a result either of insufficient hæmoglobin or of the modification of hæmoglobin so that it cannot combine with oxygen; such a state exists in carbon monoxide poisoning.

To these three types, Peters and Van Slyke[2] added a fourth, the *histotoxic* variety. In this form, due to some deleterious influence, the cells cannot use the oxygen made available to them. Alcohol, narcotics and certain poisons such as cyanide are capable of producing this type of anoxia.

Contributions to the neurological literature concerning the effects of these various kinds of anoxia on the central nervous systems of both man and animals have been gradually accumulating during the past few decades and the whole subject has recently been reviewed fully by Hoff, Grenell and Fulton.[3] However, neuropathological studies of human cases in which delayed death has followed asphyxia due to respiratory obstruction (anoxic anoxia) are not frequently reported. For this reason it is felt that the present case might be of interest.

REPORT OF A CASE

The patient, a 48-year old man of Czech origin, was admitted to hospital with gradually increasing symptoms of hyperthyroidism of one year's duration. On admission moderate bilateral exophthalmos and a diffusely enlarged gland were found; the basal metabolic rate was +50 and the total plasma cholesterol 114 mgm. %. A five week trial of thiouracil in full dosage resulted in no symptomatic or metabolic improvement, so he was transferred to the surgical service. Here, after two weeks' iodization, a subtotal thyroidectomy was done. The operation was completed without incident. His recovery from the anæsthetic was satisfactory and his general condition considered good.

At 6.00 a.m. of the first postoperative day, the patient suddenly developed moderately severe respiratory distress accompanied by cyanosis. When seen a few minutes later, he was found to have stopped breathing altogether and was very cyanosed. He was given respiratory stimulants and a tracheotomy was done through the thyroidectomy wound. No hæmatoma was found in the depth of the wound, nor was any other apparent cause of respiratory obstruction present. The patient's heart action continued strongly and he was given artificial respiration until spontaneous breathing commenced some 30 to 45 minutes after resuscitative procedures were instituted. It was estimated afterwards that the patient was completely anoxic for at least five minutes.

Some two hours after breathing had been re-established, it was noted that the patient had developed what were described as moderately severe clonic spasms of the extremities associated with opisthotonos, lasting but a few seconds and recurring frequently. These were only partially controlled by intravenous sodium pentothal and finally a solution of sodium amytal was given by continuous drip. On examination at this time the patient was unconscious, with symmetrically increased deep reflexes and bilaterally down-going plantar responses. The convulsions continued with lessened frequency and between them the patient's state could best be described by the word "vegetative". On the fifth postoperative day the convulsions again became more frequent and severe and his temperature began to rise, reaching 106.0° F. (rectal) on the day of his death which occurred 10½ days following the period of respiratory failure. Autopsy, done 8 hours after death, showed only a fairly recent bronchopneumonia in both lung bases. The epiglottis was found to be "long, flaccid, 'U'-shaped and abnormally mobile"; the path-

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ologist considered this the most likely cause of the patient's postoperative respiratory obstruction. The brain was placed in 10% formalin and was sent to Professor Eric Linell, Division of Neuropathology, Banting Institute. The spinal cord was not removed.

Gross examination of the brain (Professor Linell).—The brain weighed 1,320 gm. at the time of removal from the skull. The basal cerebral vessels appeared normal. The pons was more prominent than usual. There was slight herniation of the hippocampal unci and cerebellar tonsils. The convolutions over the vertex were rounded by œdema. Section of the brain revealed only moderate œdema of the cerebral hemispheres and cerebellum. There was severe congestion in the posterior hypothalamic regions. Blocks were taken from various areas and stained with hæmatoxylin and eosin, Mallory's connective tissue stain, Mallory's phosphotungstic acid stain, cresyl violet, Scharlach R, Smith and Quigley's modification of the Weigert stain and Cone and Penfield's silver carbonate method.

Microscopical findings.—The most important changes in the brain of this patient were found in the cerebral cortex and putamen. Moderate to severe œdema and congestion, with occasional leakage from small vessels into their perivascular spaces, were present throughout, least noticeable in the lower brain-stem.

In the cerebral cortex, pronounced degenerative changes of a laminar type were present; these were not seen in all areas examined, however. In the cortex of the frontal lobe the cells of the most superficial laminæ (II and III) almost without exception were shrunken and pyknotic with darkly-staining cytoplasm and, in cresyl violet, their nuclei stained a deep blue and were triangular in shape. The apical dendrites of many of these cells appeared thicker and stained more deeply than usual and some were tortuous. In the deeper layers of the frontal cortex, œdema of nerve-cells was the outstanding feature. Both cell body and nucleus were swollen and vacuoles were present in both. Nuclear and cellular margins were ill-defined and the cells stained poorly. Neuronophagia was slight and many of the oligodendroglia were swollen. The astrocytes showed no significant reaction and microglial histiocytes were not present. The small vessels appeared normal and the subcortical white matter showed little change apart from œdema.

In the precentral gyrus of both sides very severe changes were noted. These varied from block to block,

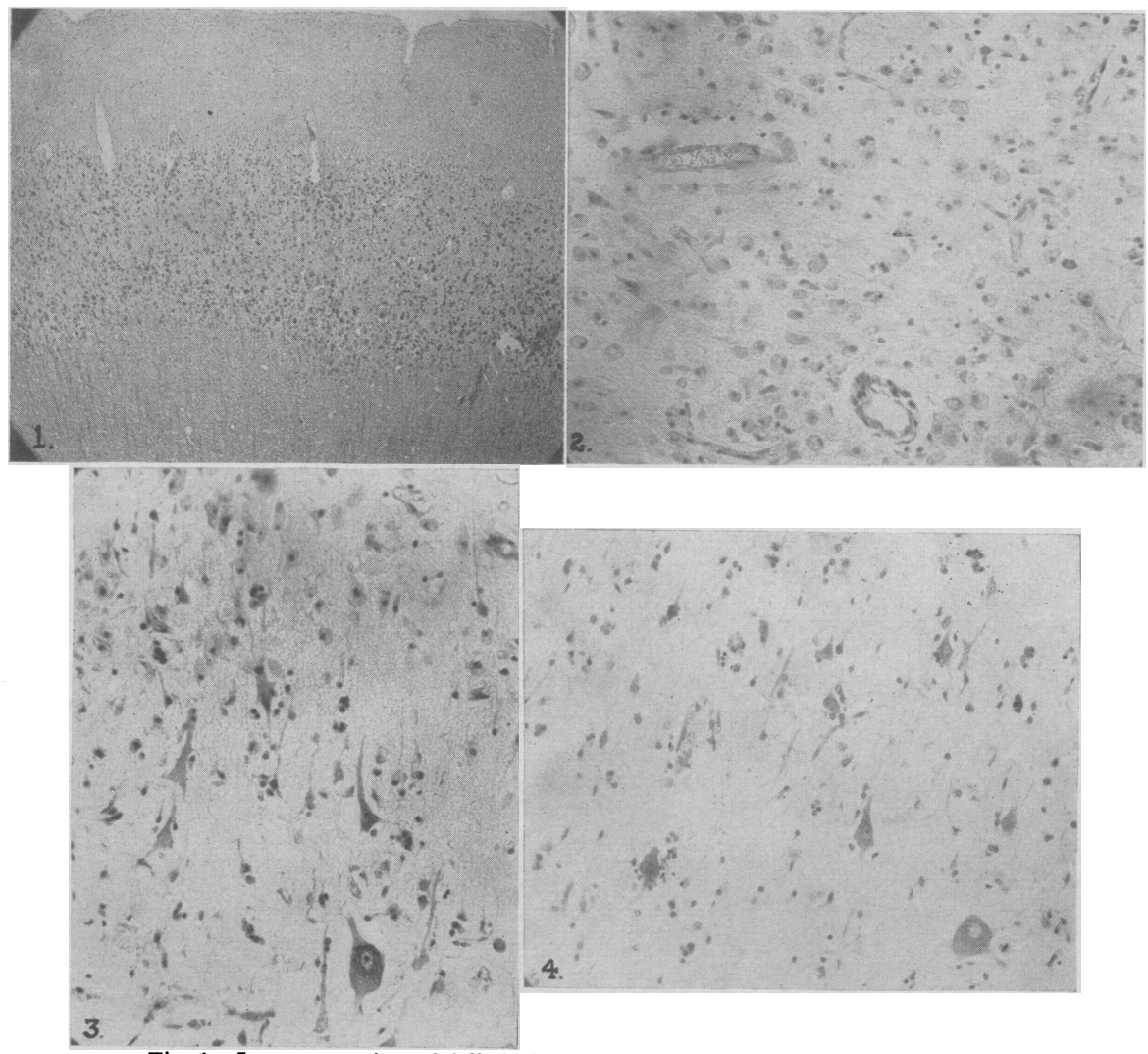


Fig. 1.—Low power view of full thickness of right precentral cortex showing cerebral histiocytes in middle layers (Scharlach R). **Fig. 2.**—Cerebral histiocytes in lamina III of precentral cortex. No nerve cells are seen (cresyl violet; x 260). **Fig. 3.**—Transition from laminæ IV to V, precentral cortex. Note that histiocytes are present in IV only. Severely degenerate large pyramidal cells in lamina V (cresyl violet; x 190). **Fig. 4.**—Neuronophagia and chromatolysis of large pyramidal cells, lamina V, precentral cortex (cresyl violet; x 165).

but were consistently present and most marked in layers III and IV and the superficial part of layer V. In these layers all nerve cell elements, astrocytes and oligodendroglia had almost completely disappeared, together with the tangential and radiating myelinated fibres characteristic of the cortex. All were replaced with abundant swollen, fat-filled cerebral histiocytes, (gitter cells) which stained well with Scharlach R and were confirmed with cresyl violet and silver carbonate (Figs. 1 and 2). Superficial to this destruction the nerve cells resembled those of the frontal cortex and, in the layers deep to the necrosis, the majority of the cells showed similar pyknotic and œdematous change with pronounced neuronophagia. Some Betz cells appeared normal but the majority showed varying degrees of chromatolysis and around some of them neuronophagia was in progress (Figs. 3 and 4). In the middle cortical layers some of the microglia had assumed rod forms. These changes were all more marked in the cortex bordering the central fissure than in that covering the convex surface of the gyrus. The histiocytes always stopped in or just external to the Betz cell layer. Many of the small vessels of these regions were distended and showed swelling of their lining endothelium. The myelin of the deeper cortical layers showed degenerative changes in the form of swelling, beading and breaking up into fine droplets (Fig. 5). The astrocytes of the white matter and the interfascicular oligodendroglia were increased in number.

In the parietal cortex, nerve cell and glial changes were very slight; in the nerve cells œdema was more marked a feature than pyknosis. Histiocytes were seen in the leptomeninges overlying the visual cortex. In the visual cortex itself, the cells of layer IV had almost completely disappeared and the whole layer was infiltrated with gitter cells. This infiltration was not as heavy as in the precentral region. Superficial and deep to this layer, nerve cell changes of a much less marked degree were noted. In the cortex of the hippocampal gyrus, œdema and vacuolation of cells were fairly frequent, but there was no laminar distribution in these changes nor was there any apparent cell loss. Most of the neurons of the insular cortex appeared normal. In the gray matter of the claustrum, many nerve cells contained free fat and gitter cells were present in moderate numbers.

The caudate nucleus showed little abnormality beyond some pyknosis or œdema of its cells. In the putamen, interstitial œdema was more severe than anywhere else in the brain (Fig. 6). Many nerve cells had disappeared and the vast majority of those remaining were severely shrunken. Fat-filled cerebral histiocytes were frequent, often grouped around perivascular spaces (Fig. 7). The small vessels of the putamen presented a strik-

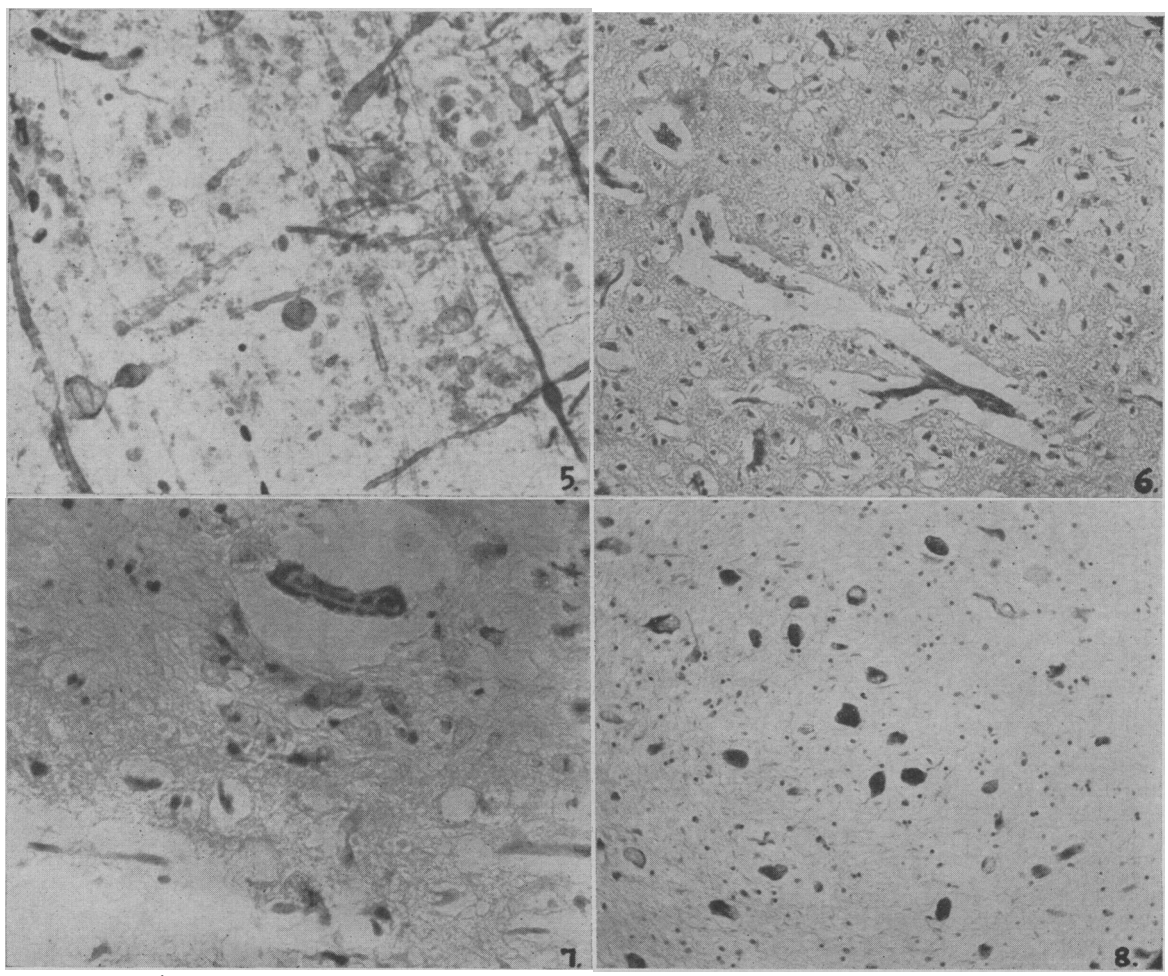


Fig. 5.—Degenerative changes in myelin, precentral subcortical white matter; swelling, irregularity and breaking-up of myelin sheaths (Smith and Quigley; x 320). **Fig. 6.**—Right putamen. Extreme œdema. Complete absence of nerve cells and necrosis of vessel walls (cresyl violet; x 190). **Fig. 7.**—Right putamen. Cerebral histiocytes grouped around a perivascular space which contains a necrotic vessel (cresyl violet; x 390). **Fig. 8.**—Right globus pallidus. Nerve cells present, although degenerate; histiocytes absent (cresyl violet; x 190).

ing appearance. The walls of many of them appeared definitely necrotic, being smudgy and featureless and staining unusually deeply with cresyl violet and hæmatoxylin and eosin. Their endothelial cells were pyknotic and the lumina of most were practically obliterated by collapse of their walls. Very few contained any blood cells. The astrocytes of the putamen were swollen. The cells of the globus pallidus showed much less severe change. Many of them were hyperchromatic and others were filled with fat which pushed the contents of the cell to one side. The vessels here appeared normal and no glitter cells were seen (Fig. 8).

There was little alteration in the nerve cells of the hypothalamus. Hæmorrhage had occurred into some of the perivascular spaces of the subependymal vessels in the posterior hypothalamus. In the midbrain the cells of the oculomotor nuclei showed little departure from normal nor did those of the substantia nigra. The cells of the superior colliculus and red nucleus showed moderate changes similar to those already described. In the pons, petæchial hæmorrhages were present under the floor of the fourth ventricle. One was present in the left VIth nerve nucleus. Many of the cells of these nuclei were shrunken. The cells of the VIIth nerve nucleus contained various sized collections of lipochrome pigment and varying degrees of chromatolysis. The tissue of the pontine tegmentum showed severe œdema. The cellular changes in the medulla were not notable.

In the cerebellar cortex, the molecular and granular layers appeared normal. In some areas marked œdema separated these strata. The Purkinje cells appeared moderately reduced in numbers. Many of those remaining stained palely and showed poor nuclear definition. The occasional cell was undergoing neuronophagia (Fig. 9). The neurons of the dentate nucleus showed uniform pallor and some were reduced to homogeneous masses of cytoplasm without evidence of nuclei. The white matter of the cerebellar centrum was very œdematous and severe degenerative changes were evident in the myelin (Fig. 10).

In summary, nerve cell changes were the most noticeable histopathological feature in this brain. These varied in severity from area to area and were most marked in layers III and IV of the cortex of the precentral gyri bilaterally, in layer IV of the visual cortex, in the gray matter of the claustrum and in the putamen. In all of these areas, actual softening had taken place and gitter cells were present in varying numbers. Astrocytes and oligodendroglia showed degenerative changes, or had completely disappeared from these areas. Changes were considered moderate in the frontal, parietal and hippocampal cortex, the caudate nucleus and globus pallidus, the thalamus, superior colliculus and red nucleus and the Purkinje cells and dentate nucleus of the cerebellum. The cells of the majority of the nuclei of the pons and medulla showed mild changes. The oculomotor nuclei, substantia nigra and hypothalamus presented little departure from normal.

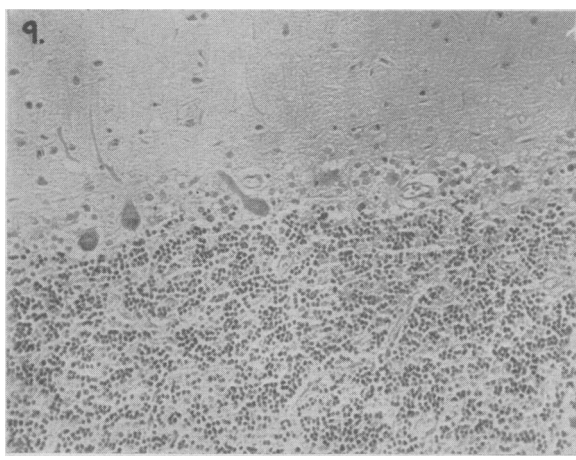
Apart from some swelling and some proliferation of endothelial cells, the majority of the small vessels presented no significant abnormality. In the putamen, however, they appeared necrotic. The most severe myelin changes were seen in the deeper cortex of the precentral gyri, the subcortical white matter underlying these, and the deep cerebellar centrum.

In studying the changes described above, the frequency of postmortem and fixation artefacts in the human nervous system was kept in mind; the areas studied were carefully compared with the same regions in the brains of patients who had died as a result of pathological states outside the nervous system.

SUMMARY OF A REVIEW OF THE LITERATURE

1. *Human material.*—Detailed examinations of the brain in cases dying at some interval after a period of severe respiratory obstruction are rare. Helwig[4] in 1937 described his findings in a patient who developed tracheal obstruction by a blood-clot following a block dissection of the neck. Respirations were arrested for ten minutes. He died, with increasingly severe convulsions, three hours after tracheotomy had relieved the obstruction. Diffuse degenerative changes were found in cortical nerve cells, with free fat in some large pyramidal cells. The author described fat-containing phagocytes in perivascular spaces. The basal ganglia were normal.

Cases of survival for 80 and 96 hours respectively, after attempted suicide by hanging, have been investigated by Dublin and Brown[5] and Doring.[6] Severe nerve cell degeneration in cerebral cortex, basal ganglia and in the Purkinje cells of the cerebellum are described in both these brains. Dublin and Brown state that layers III and IV of the cerebral cortex



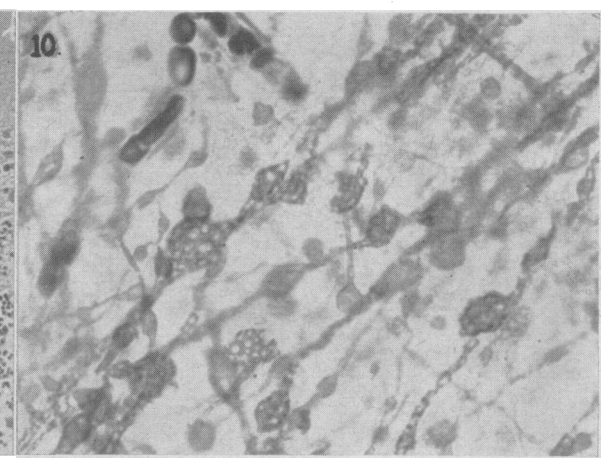


Fig. 9.—Cerebellar cortex. Degenerative changes in Purkinje cells. Some are undergoing neuronophagia (cresyl violet; x 175). **Fig. 10.**—Cerebellar white matter. Swelling, beading and breaking-up of myelin sheaths (Smith and Quigley; x 660).

were those most severely affected. Doring considered the putamen to be the most severely involved region in his case.

These three cases suggest a gradient of degree of injury when different regions of the brain are compared. The cells of the cerebral cortex, particularly those of the middle layers, are most susceptible to anoxia. The basal ganglia are almost as severely involved, the putamen and globus pallidus showing greater damage than the caudate nucleus.

Courville[7] has reviewed a series of 9 fatalities from anæsthetic accidents, mainly by nitrous-oxide-oxygen mixtures, the survival times of these patients varying from forty hours to twenty-six days, and O'Brien and Steegman[8] describe the cerebral changes in a patient who survived for 16 months in a state of decerebrate rigidity after a period of apnœa, while under nitrous-oxide-oxygen anæsthesia. In both these reports the nerve-cells of the cerebral cortex and of the basal ganglia showed severe degeneration, particularly marked in layers III and IV of the cortex. The cerebellum was not mentioned by O'Brien and Steegman but Courville describes degeneration of Purkinje cells in his cases.

Two fatalities from anoxia caused by low oxygen tension of the inspired air in high altitude flying are described in U.S.A.A.F. air crew by Titrud and Haymaker.[9] These men survived for 40 hours and for 21 days respectively, and here again the oxygen lack produced severe degeneration in the cortical nerve cells, particularly in the middle layers. The caudate nucleus and the putamen were more degenerate than the globus pallidus. Purkinje cells of the cerebellar cortex were severely degenerate.

Stewart[10] in 1920 and Wilson and Winkleman[11] in 1925 have shown laminar cortical degenerative changes in layers III and IV in cases of carbon monoxide poisoning surviving, respectively, 24 and 17 days.

2. *Experimental studies.*—Gildea and Cobb,[12] Weinburger, Gibbon and Gibbon,[13] Kabat and Dennis[14] and Grenell[15] have all produced stagnant cerebral anoxia in experimental animals, using different methods to interrupt the arterial circulation to the brain.

All these experimentalists agree as to the vulnerability of the cortical nerve cells and, in particular, those of laminæ III and IV, to circulatory arrest. They differ in their estimates of the minimum time required for the production of irreversible cortical nerve cell damage. Grenell believes that in certain areas of the cortex, irreversible cell changes occurred after as short a period as two minutes. Weinburger, Gibbon and Gibbon found irreversible cell changes consistently after an arrest of 3½ minutes. They considered that the cortex of the motor and the visual areas was the most vulnerable and these changes were visible microscopically 4½ days after circulatory arrest of 7½ minutes. The Purkinje cells of the cerebellum were almost as vulnerable as those of the cerebral cortex. They also concluded that six to seven minutes of circulatory arrest was necessary to produce changes in the basal ganglia nerve cells comparable with those produced in the cortical cells in half that time. They found other nuclear masses to be much less susceptible and the spinal cord was found to be uniformly normal regardless of the duration of the circulatory arrest. Gildea and Cobb confined their observations to the cerebral cortex. They were able to see histological changes in the cells of the middle cortical laminæ 24 hours after a possibly incomplete arrest of the cerebral blood flow for 10 minutes.

DISCUSSION

In reviewing the above human cases and animal experiments it becomes apparent that the central nervous system changes induced by the stagnant, anoxic and anæmic types of anoxia are very similar. It will be noted that the cerebral cortex is especially vulnerable and that, as the duration increases, the damage becomes more marked. Laminæ III and IV, especially in the precentral and calcarine areas, appear most sensitive. The lenticular nucleus appears almost equally susceptible, although as a result of carefully controlled experimental work,[13, 15] it appears that twice the duration of anoxia must be present before the cells of this region show changes comparable to those seen in the middle cortical layers. The Purkinje cells of the cerebellum likewise share this extreme sensitivity. Should the process be sufficiently severe and the patient's survival prolonged, evidence of actual softening will be seen in the presence of fat-filled cerebral histiocytes and, later still, in the proliferation of new capillaries. It is probable that at least four days must elapse before histiocytes appear in the softened areas; Helwig's[4] finding them already present after survival of

only a few hours is open to doubt. Changes of lesser severity are seen in various diencephalic and brain-stem nuclei. The somatic efferent and special visceral efferent cells of the brain-stem, like those of the spinal cord, appear to be resistant to a rather high degree of oxygen lack.

The fact that the cellular changes outlined in these three types of anoxia are so similar, suggests that a common mechanism may be at work. Vascular factors might well play a part in this mechanism. To become more speculative, the metabolic rate of the cells in question might be of importance. Craigie[16] has shown that lamina IV is the most vascular layer of the cerebral cortex of the albino rat and that lamina II is only slightly less so. The capillary density of the remaining layers tapers off progressively as one approaches either the surface or the subcortical white matter. In another study, Craigie[17] found that the sensory and correlation centres of the brain-stem possessed a more rich vascular supply than that possessed by the motor nuclei. These observations on capillary density can be correlated in a general way with the pathological changes in anoxia referred to above. In a series of somewhat similar studies of the cat's brain Dunning and Wolff[18] felt that they were able to demonstrate that the vascularity of a given region is a function of the number of synapses contained in that region. As to the vascularity of the parietal cortex of the cat, these authors found that lamina IV possessed the greatest number of capillaries per unit area, and that it was closely followed by laminæ III and II. They also estimated that the number of capillaries present in the cat's parietal cortex is over twice as great as in the parietal white matter or trigeminal nerve, over half as great as in the trigeminal ganglion, and only slightly greater than in the superior cervical ganglion. In the trigeminal ganglion there is a one to one ratio between entering nerve fibres and cell bodies; being a sensory ganglion, the fibres pass right through and there are no synapses. On the other hand, Ranson and Billingsley[19] have shown that in the cat's superior cervical ganglion there is a ratio of thirty-two cell-bodies to each fibre in its preganglionic nerve; hence many synaptic structures are present. On the basis of his comparative anatomical studies, Kappers[20] concluded that the granular layer of the cortex (IV) "is primary in character and has originally receptive functions". He conceived of the infragranular layers (V and VI) as having chiefly the functions of projection and inter-regional association. The supra-granular layers (II and III), which phylogenetically have appeared most recently, have to do with inter-regional associations of a higher order.

From these observations, it is but a step to assume a quantitative relationship between vascularity and metabolic activity in various regions of the nervous system. The studies of Holmes[21, 22] have shown that the cerebral cortex consumes more oxygen than either white matter or peripheral nerve. Dixon and Meyer[23] have placed the trigeminal ganglion in the same category as white matter and peripheral nerve on the basis of its oxygen consumption and this again correlates fairly well with its relative vascularity. Proceeding on a *post hoc propter hoc* line of reasoning, one might assume that the basis of the specific vulnerability of the middle layers of the cerebral cortex lies in the richness of the synaptic network and the large cell population per unit volume of tissue in this region, implying, as this does, a higher rate of cellular metabolism. The presumed function in these layers also fits in with this explanation. Carrying on with this line of thought, it seems not unreasonable that the regions with the highest metabolic rate should be most susceptible to the effects of oxygen-lack and the disturbances in cellular oxidative processes which accompany it. Wolff[24] supports the assumption that there is a quantitative relationship between vascularity and metabolic activity in the brain. Elsewhere, Wolff[25] states that vascularity varies with the number of synaptic structures present rather than with differences in the number or mass of nerve cell bodies. On the other hand, Grenell and Kabat[26] have found the cells of the supraoptic and paraventricular nuclei of the hypothalamus, whose vascularity is richest of any region of the entire brain (Craigie[27]), are highly resistant to anoxia. This may be a rather special case, however, and Grenell and Kabat postulate that these nuclei may regulate water metabolism as a result of direct stimulation by the blood stream rather than through the presence of afferent nerve endings.

It is with not a little diffidence that one supports such an hypothesis, based in part at least upon speculation, to account for the high degree of vulnerability to anoxia shown by specific areas of the nervous system. It is probable that many will disagree with this idea in principle

and subsequent investigations may prove it untenable. Indeed, already Grenell and Kabat[26] feel that the degree of vascularity of a certain region is no index of its susceptibility to anoxia.

Finally, I would like to add that limitations of space preclude any discussion of the central nervous system changes in "irreversible hypoglycæmia" beyond their mere mention. In reviewing reported studies of this state,[28 to 32] one is struck by the similarity of the histopathological picture it presents to that detailed above. This is not surprising when one considers that the disturbance in hypoglycæmia is essentially an intracellular anoxia with inability to use oxygen due to lack of available substrate, glucose. By broadening our concept of "histotoxic anoxia" somewhat, insulin in excess might be regarded as a toxin.

SUMMARY

The histopathological changes occurring in the brain of a man deprived of oxygen for a period of between five and ten minutes are described. The most severe changes were found in the cerebral cortex, particularly in the motor and visual areas, in the putamen and in the cerebellum. In both the precentral and visual cortex, a striking band of softening containing compound granular corpuscles was found. Here and elsewhere nerve cell and blood vessel changes of varying degrees of severity were seen. The entire pathological picture supports a concept of variation in the susceptibility of different areas of the brain to oxygen lack. The possible significance of this variation is discussed and a portion of the pertinent literature is reviewed.

I wish to thank Professor Eric A. Linell, Division of Neuropathology, University of Toronto, for permission to publish the pathological findings and for the help he has given me in the preparation of this paper. I also wish to thank Dr. Noble Sharpe, Pathologist to the Toronto Western Hospital, for access to the clinical and autopsy records.

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ESSENTIAL BROWN INDURATION OF THE LUNGS

(Idiopathic Pulmonary Hæmosiderosis)

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ESSENTIAL brown induration of the lungs (idiopathic pulmonary hæmosiderosis) has recently been reviewed by Wyllie[1] and his colleagues at Great Ormond Street, London. The condition was first described in 1931 and the reviewers present 17 cases from the world literature and a series of 7 of their own. Only two of the cases quoted are from the North American continent. While admittedly a rare condition, it is noteworthy that, of the 24 recorded cases, 16 are the work of five groups of authors. Accordingly one could justifiably assume that the diagnosis is usually missed. The condition is not familial and has been encountered in children from a few months to 16 years of age. It is characterized by periodic attacks of tachycardia, pyrexia, pallor, fatigue, cyanosis, increasing dyspnœa, signs of congestive cardiac failure, severe anæmia with signs of active blood regeneration, and hæmoptysis. Pulmonary findings in life are usually more conspicuous radiologically than clinically. Between attacks the subject may remain well but commonly there is chronic ill-health. The condition ends fatally